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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,638	02/08/2002	Tim Wilhelm Nattkemper	MULL-021XX	5891

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WEINGARTEN, SCHURGIN, GAGNEBIN & LEBOVICI LLP
TEN POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER	
LAVIN, CHRISTOPHER L	
ART UNIT	**PAPER NUMBER**
2624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/869,638	NATTKEMPER ET AL.	
	Examiner	Art Unit	
	Christopher L. Lavin	2624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-9,11,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-9,11,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response the RCE filed on 03/12/07.

Claim Rejections - 35 USC § 103

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1, 2, 5 – 9, 11, 13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Luck (5,257,182), Watanabe (5,522,015), and Hemstreet (5,733,721).

In regards to claim 1, Luck discloses a method for analyzing microscope images comprising of the following steps:

a) Taking at least two microscope images of a sample including a plurality of biological objects (col. 4, lines 13 – 19);

b) Selecting a first microscope image and marking the positions (s) of mass gravity centers, i.e., centroids, of a number n of the individual objects discernible in the first microscope image, in which step each marked object is assigned a defined first image excerpt which completely surrounds the marked object, and each first image excerpt including a marked object, and each first image excerpt including a marked object is assigned the value 1, with the number n of such marked first image excerpts constituting a positive training set (col. 7, lines 46 – 53; col. 13, lines 17 – 23: Two training sets are disclosed, malignant and benign with a 0.9 and 0.1. Luck does not disclose using 1 and 0 for training a neural network. This will be shown to be well known in the art through Watanabe below. A complete training set consists of a positive (1) and

a negative (0) training set; col. 13, lines 40 – 48: the training set is based on "precisely the same type of net images" as were obtained for classification.);

c) Selecting and marking a number m of second image excerpts in said first microscope image each spaced a predetermined minimum distance from said first image excerpts, with a second image excerpt corresponding in size and shape to said first image excerpt, in which step each second image excerpt is assigned the value 0, with the number m of such marked second image excerpts constituting a negative training set (col. 7, lines 46 – 53; col. 13, lines 17 – 23; col. 8, lines 49 – 62; col. 13, lines 40 – 48: Two training sets are disclosed, malignant and benign with a 0.9 and 0.1. The training excerpts are chosen in exactly the same manner as the excerpts to be analyzed. Luck discloses that the image is processed to remove all objects larger than the objects of interest. So cell clumps will be removed; thus the only thing that will remain in the image after the processing is individual cells. Therefore cells that are touching would not remain. So only separate cells (at least 1 pixel of separation) will remain in the image, and therefore a minimum predetermined distance (1 pixel) is maintained between the first image excerpts and the second image excerpts.);

d) Determining characteristic features and/or feature combinations of the positive and negative training sets and assigning said characteristic features and/or feature combinations to a classification value between 0 and 1; said classification value representing the degree of probability of the presence of a marked object, and the determined features and/or feature combinations are stored (On page 7 of the applicant's remarks it is noted that step d is disclosed "at the top of p. 10 and continuing

for the rest of the page". Although step d is broad enough to cover the examiner's previous rejection, where the examiner believed that the content of page 9 described step d, in order to speed prosecution the examiner will provide a rejection that takes into account more clearly what the applicant views as what claim d is calling for. Therefore, based on the reading of page 10 in the specification it appears the applicant is simply describing the operations of a neural network. Where the classification value is in reference to the output of the neural network. Luck clearly discloses that the neural network is trained in exactly the same way as it used (col. 13, lines 40 – 48) and that the neural network outputs a classification value between 0.1 and 0.9, a 103 combination will be provided below teaching that a range of 0 to 1 could be substituted for the 0.1 to 0.9 range taught by Luck. It should be noted that although Luck does use more than one image to train the neural network, Luck does need to start with one image who's feature classifications will affect the classifications of all subsequent classifications by the neural network.);

e) Determine classification values of all image points of the second and each further microscope image by comparing the image data of the second and each further microscope image with the features and/or feature combinations in said first microscope image determined in procedural step d), in which step, for each image point of the second and each further microscope image, the classification value for an image excerpt surrounding the image point is determined and the size and shape of this image excerpt corresponds to the size and shape of the first or second image excerpt (col. 13, lines 17 – 23);

f) recognizing the position(s) of biological objects in the second or each further microscope image by evaluating the determined classification values, in which step the determined classification values are compared with a given threshold value representing the presence of a biological object, wherein classification values of all mage points of the second and each further microscope image are automatically determined according to the procedural step e) by scanning the image surface of the second and each further microscope image and wherein, further, the object positions determined by procedural steps a) to f) are compared in the total number of microscope images so as to obtain a spatial location and distribution of the individual objects in the sample (col. 14, lines 3 – 7; col. 14, lines 30 – 35);

[and wherein the biological objects to be determined are marked with a different set of one or plural chemical makers before each microscope image is taken, and bleaching or rinsing procedure is performed between taking the next image].

Luck does not disclose using 1 and 0 for training a neural network. However, Watanabe (col. 5, lines 59 – 61) discloses using 1 and 0 to train a neural network. Luck discloses a method capable of classifying biological specimens on a microscope slide, however Luck has not specifically claim a threshold. However, Watanabe (col. 25, lines 42 – 44) discloses using a threshold of 0.5 to separate neural network outputs into two possibilities.

Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to use 0 and 1 to train a neural network as taught by Watanabe instead of 0.1 and 0.9 as taught by Luck. As the intent is to separate two types allowing

more separation between the types will allow for better thresholding. Also to use thresholding for classification of neural network outputs (as disclosed by Watanabe) in the method disclosed by Luck allows for separation of the data into two subsets, as Luck's method is designed to classify a cell as either malignant or benign thresholding will quickly and easily separate outputs for easy analysis.

The newly added claim language [03/12/07] calls for a well known procedure called double-labeling, where one stain is applied to a slide, the slide is rinsed, and then a second different stain is applied to the slide. As previously discussed in the office action dated 07/13/06:

> Hemstreet teaches that slides should be rinsed (col. 28, lines 27 – 32) before staining. Hemstreet then teaches that to create fluorescent images requires staining the slide with a fluorchrome (col. 7, line 64 – col. 8, line 6). Hemstreet then analyzes the fluorescent images with a neural network (col. 7, lines 47 – 51).

Hemstreet also teaches that double-staining be performed (col. 8, lines 16 – 40) on the slides.

Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to prepare and stain the microscope slide (as taught by Hemstreet) before analyzing the microscope slide (as taught by Luke). A slide needs to be prepared in advance of use if the results are to be trusted. By staining the slide the method disclosed by Luke will have an easier time of identifying cells of interest. Finally double-

labeling is a well known approach which allows for more cell detail to be brought out, which would only help Luck in identifying cell structures.

With regards to claim 2, the method as claimed in claim 1 wherein the sample is a tissue sample and the biological object is a cell (Luck, col. 8, lines 33 – 35).

With regards to claim 5, the method as claimed in claims 3 wherein said chemical markers are fluorochrome markers and the microscope images are fluorescence images (Hemstreet, col. 7, line 64 – col. 8, line 6).

With regards to claim 6, the method as claimed in claim 1 wherein the microscope images are taken by a CCD camera and then digitized (Luck, col. 7, lines 11 – 13).

With regards to claim 7, the method as claimed in claim 1 wherein the number n of the individual biological objects marked in procedural step b) is larger than or equal to 50 (Luck, col. 13, lines 17 –19: As "several hundred or thousands" of cells are used to create a training set inherently at least 50 of these biological objects would represent the positive (malignant) case.).

With regards to claim 8, the method as claimed in claim 1 wherein the first image excerpt is of square shape, with the size and/or side length of the first image excerpt corresponding at least to the maximum diameter of the biological objects in the first microscope image (Luck, col. 7, lines 49 – 59).

With regards to claim 9, the method as claimed in claim 1 wherein the number n of second image excerpts is larger than or equal to 50, with the second image excerpts being defined automatically, keeping to the minimum distance from the respective first

image excerpts (Luck, col. 13, lines 17 – 19: As "several hundred or thousands" of cells are used to create a training set inherently at least 50 of these biological objects would represent the negative (begin) case).

With regard to claim 11, the method as claimed in claim 1 wherein the threshold value of the classification value representing the presence of a biological object is at least 0.5 (Watanabe, Col. 25, lines 42 – 44).

With regards to claim 13, A method as claimed in claim 1 wherein fluorescent cells in said sample are automatically classified (Luck, col. 3, lines 38 – 39; Hemstreet, col. 7, line 64 – col. 8, line 6).

With regards to claim 15, the method as claimed in claim 4 wherein said chemical markers are fluorochrome markers and the microscope images are fluorescence images (Hemstreet, col. 7, line 64 – col. 8, line 6).

Response to Arguments

4. Applicant's arguments filed 03/12/07 have been fully considered but they are not persuasive.

5. The applicant's primary argument is that the new material in claim 1 overcomes the rejection of Luck, Watanabe, and Hemstreet. However, as described in the rejection of claim 1 the applicant is now claiming a common process known as double-labeling, which Hemstreet does teach. Therefore the examiner is maintaining the previous rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher L. Lavin whose telephone number is 571-272-7392. The examiner can normally be reached on M - F (8:30 - 5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bhavesh M. Mehta can be reached on (571) 272-7453. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christopher Lavin

BHAVESH M MEHTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 2600